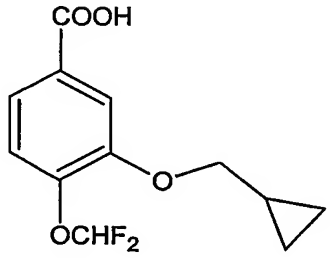
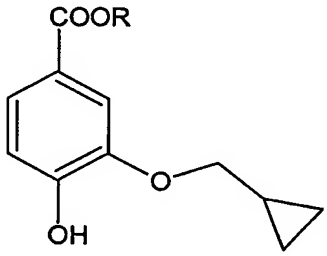
We claim:

1. A process for the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid of Formula I,



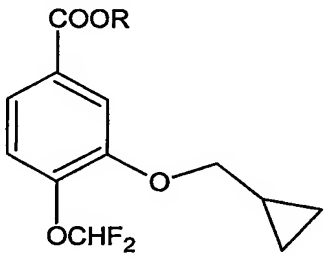
FORMULA I

the process comprising reacting compound of Formula II,



FORMULA II

wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl, with difluoro methylating agent in the presence of a base to obtain compound of Formula III,



FORMULA III

wherein R is as defined above; and desterification of the compound of Formula III to obtain the compound of Formula I.

2. The process of claim 1, wherein R represents methyl or ethyl.

3. The process of claim 1, wherein the difluoromethylating agent comprises one or more of difluorochloromethane (Freon-22®) and alkyl difluorochloroacetate.

4. The process of claim 3, wherein the alkyl difluorochloroacetate comprises one or more of methyl difluorochloroacetate, ethyl difluorochloroacetate and tertiary butyl difluorochloroacetate.

5. The process of claim 1, wherein the base comprises one or more of inorganic and organic bases.

6. The process of claim 5, wherein the organic base comprises one or more of trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, DBU (1,8-diazabicyclo- [5.4.0]-undec-7-ene), DBN (1,5- diazabicyclo-[4.3.0]-non-5-ene), and 4-dimethylamino pyridine.

7. The process of claim 5, wherein the inorganic base comprises one or more of alkali metal carbonates, alkali metal bicarbonates and alkali metal hydroxides.

8. The process of claim 7, wherein the alkali metal carbonate comprises one or more of lithium carbonate, sodium carbonate and potassium carbonate.

9. The process of claim 7, wherein the alkali metal bicarbonate comprises one or both of sodium bicarbonate and potassium bicarbonate.

10. The process of claim 7, wherein the alkali metal hydroxide comprises one or both of sodium hydroxide and potassium hydroxide.

11. The process of claim 1, wherein the reaction is carried out in the presence of a phase transfer catalyst.

12. The process of claim 11, wherein the phase transfer catalyst comprises one or more of quaternary ammonium salts and quaternary phosphonium salts.

13. The process of claim 12, wherein the quaternary ammonium salt comprises one or more of tetramethyl ammonium iodide, tetrabutyl ammonium iodide, benzyltributyl ammonium bromide, 1-methylpyridinium iodide, tetramethyl-2-butylammonium chloride, trimethylcyclopropylammonium chloride, tetrabutylammonium bromide, and t-butylethyldimethylammonium bromide.

14. The process of claim 12, wherein the quaternary phosphonium salt comprises one or more of tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutyl phosphonium bromide, benzyltriphenyl phosphonium bromide, and tetraphenyl phosphonium chloride.

15. The process of claim 1, wherein the reaction is carried out in a solvent.

16. The process of claim 15, wherein the solvent comprises one or more of alkyl ethers, alcohols, ketones, chlorinated hydrocarbons, esters, hydrocarbons, dipolar aprotic solvents, cyclic ethers, and nitriles.

17. The process of claim 16, wherein the ether comprises one or more of diethylether, diisopropylether and dimethoxyethane.

18. The process of claim 16, wherein the alcohol comprises one or more of methanol, ethanol, isopropanol and butanol.

19. The process of claim 16, wherein the ketone comprises one or both of acetone and methyl isobutyl ketone.

20. The process of claim 16, wherein the chlorinated hydrocarbon comprises one or more of methylene chloride, ethylene dichloride and carbon tetrachloride.

21. The process of claim 16, wherein the ester comprises one or both of ethylacetate and isopropylacetate.

22. The process of claim 16, wherein the hydrocarbon comprises one or more of benzene, xylene, toluene, hexane, cyclohexane, heptane and octane.

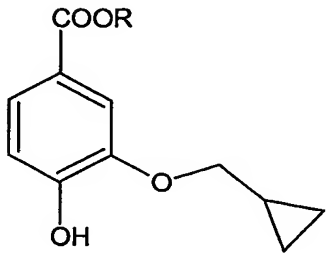
23. The process of claim 16, wherein the dipolar aprotic solvent comprises one or both of dimethylsulfoxide, and dimethylformamide.

24. The process of claim 16, wherein the cyclic ether comprises one or both of dioxane, and tetrahydrofuran.

25. The process of claim 16, wherein the nitrile comprises one or both of acetonitrile and benzonitrile.

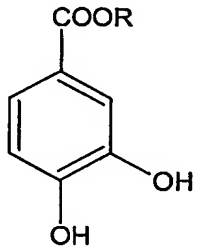
26. The process of claim 1, wherein the reaction of compound of Formula II with difluoro methylating agent is carried out at temperature of from about 25°C to about 50°C.

27. A process for the preparation of 3-cyclopropylmethoxy-4-hydroxy benzoate of Formula II,



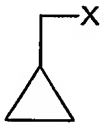
FORMULA II

wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl, the process comprising reacting 3,4-dihydroxy benzoate of Formula IV,



FORMULA IV

wherein R is as defined above with cyclopropylmethyl derivative of Formula V,



FORMULA V

wherein X is a leaving group, in the presence of a base.

28. The process of claim 27, wherein R represents methyl or ethyl.

29. The process of claim 27, wherein the base comprises one or more of inorganic and organic bases.

30. The process of claim 29, wherein the organic base comprises one or more of trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, DBU (1,8-diazabicyclo- [5.4.0]-undec-7-ene), DBN (1,5- diazabicyclo-[4.3.0]-non-5-ene), and 4-dimethylamino pyridine.

31. The process of claim 29, wherein the inorganic base comprises one or more of alkali metal carbonates, alkali metal bicarbonates and alkali metal hydroxides.

32. The process of claim 31, wherein the alkali metal carbonate comprises one or more of lithium carbonate, sodium carbonate and potassium carbonate.

33. The process of claim 31, wherein the alkali metal bicarbonate comprises one or both of sodium bicarbonate and potassium bicarbonate.

34. The process of claim 31, wherein the alkali metal hydroxide comprises one or both of sodium hydroxide and potassium hydroxide.

35. The process of claim 27, wherein the reaction is carried out in the presence of a phase transfer catalyst.

36. The process of claim 35, wherein the phase transfer catalyst comprises one or more of quaternary ammonium salts and quaternary phosphonium salts.

37. The process of claim 36, wherein the quaternary ammonium salt comprises one or more of tetramethyl ammonium iodide, tetrabutyl ammonium iodide, benzyltributyl ammonium bromide, 1-methylpyridinium iodide, tetramethyl-2- butylammonium chloride, trimethylcyclopropylammonium chloride, tetrabutylammonium bromide, and t-butylethyldimethylammonium bromide.

38. The process of claim 36, wherein the quaternary phosphonium salt comprises one or more of tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutyl phosphonium bromide, benzyltriphenyl phosphonium bromide, and tetraphenyl phosphonium chloride.

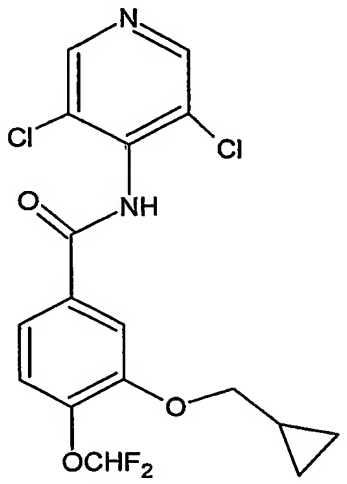
39. The process of claim 27, wherein the reaction is carried out in a solvent.

40. The process of claim 39, wherein the solvent comprises one or more of alkyl ethers, alcohols, ketones, chlorinated hydrocarbons, esters, hydrocarbons, dipolar aprotic solvents, cyclic ethers, and nitriles.

41. The process of claim 27, wherein the leaving group X in the compound of Formula V represents chlorine, bromine, iodine, sulphate and tosylate.

42. The process of claim 27, wherein the reaction of compound of Formula IV with cyclopropylmethyl derivative of Formula V is carried out at temperature of from about 25°C to about 50°C.

43. The process of claim 1, further comprising reacting an activated derivative of the compound of Formula I with 4-amino-3,5-dichloro pyridine,



FORMULA VI

to give a compound of Formula VI.

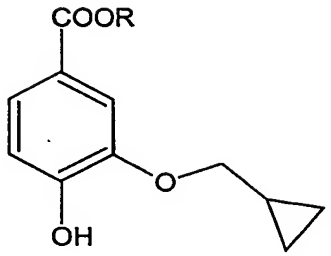
44. The process of claim 43, wherein the activated derivative is acid halide or a reactive ester of the compound of Formula I.

45. The process of claim 44, wherein the reaction of activated derivative of the Formula I with 4-amino-3,5-dichloro pyridine in carried out in the presence of sodium hydride in tetrahydrofuran.

46. A pharmaceutical composition comprising a therapeutically effective amount of roflumilast obtained by the process of claim 43; and one or more pharmaceutically acceptable carriers, excipients or diluents.

47. A method of treating asthma, inflammation, bronchitis, allergy, osteoporosis, dermatoses and disorders related to immune system, heart and kidney in a warm-blooded animal comprising administering a pharmaceutical composition that includes roflumilast prepared by the process of claim 43.

48. A compound of Formula II,

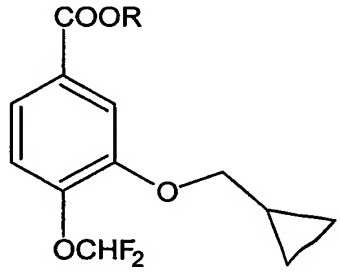


FORMULA II

wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl.

49. The compound of claim 48, wherein R represents methyl or ethyl.

50. A compound of Formula III,



FORMULA III

wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl.

51. The compound of claim 50, wherein R represents methyl or ethyl.